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Knol, H.M.; Schultinge, L.; Erwich, J.J.H.M.; Meijer, K.

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lead to DVT or PE, and require no or different treatment [7]. Finally, we used a standardized, but not validated, questionnaire to inquire about inflammatory or infectious signs. Therefore, misclassification could have occurred. Nevertheless, one should expect similar misclassification in both cases and controls.

In conclusion, this study showed that DVT was often preceded by signs of transient inflammation or infection, suggesting an association or pathogenic relationship between venous thrombosis and an underlying inflammatory or infectious disease.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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Fondaparinux as an alternative anticoagulant therapy during pregnancy

H. M. KNOL,* † L. SCHULTINGE,* J. J. H. M. ERWICH,† and K. MEIJER*

*Division of Haemostasis and Thrombosis, Department of Haematology; and †Department of Obstetrics and Gynaecology, University Medical Centre Groningen, Groningen, the Netherlands

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Correspondence: M. Knol, Department of Haematology, Division of Haemostasis and Thrombosis, University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands.
Tel.: +31 50 3612791; fax: +31 50 3611790.
E-mail: h.m.knol@og.umcg.nl

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Hypersensitivity skin reactions are frequently seen in pregnant patients who use low-molecular-weight heparin (LMWH) [1]. When this heparin intolerance occurs, alternative choices for anticoagulation are limited. Hypersensitivity skin reactions often recur when another preparation of LMWH is substituted [1]. Danaparoid is another preparation of choice which does not pass the placenta [2], but is not always available. Most patients strongly wish to avoid vitamin K antagonists, even beyond the 12th week of pregnancy, because of the association with congenital and developmental abnormalities [3,4]. Fondaparinux, a synthetic selective inhibitor of activated factor X

(FXa), is commonly used as an alternative anticoagulant in non-pregnant patients who develop heparin intolerance. Fondaparinux has been extensively studied for use in surgery prophylaxis and treatment of thromboembolic diseases [5]. However, data on the use of fondaparinux in pregnancy is limited to animal models and a few case reports [6–10]. Although it has been shown that transplacental passage can occur resulting in low measurable FXa activity in cord blood [11], no adverse outcomes in pregnancy have been reported in these four women. The other six separately published cases reported no adverse events to the mother or child [6–10]. In our hospital, experience with fondaparinux as an alternative in pregnant women has accumulated. The aim of the present study was to evaluate the use and safety of fondaparinux during pregnancy.

From 2003 until the present, we prospectively followed a consecutive cohort of 133 women in our university hospital who used anticoagulant therapy during their pregnancy and puerperium. The indication for anticoagulant therapy was a history of idiopathic, provoked or previous pregnancy-related venous thrombo-embolism (VTE) or recurrent fetal loss. Recurrent fetal loss was defined as two or more fetal losses. In all women thrombophilia screening was performed. Applied assays have been described elsewhere [12]. All women were started on a LMWH (nadroparin or tinzaparin) in early pregnancy with a body weight adjusted therapeutic dosage ($175 \text{ anti-Xa IU kg}^{-1} \text{ day}^{-1}$), as soon as a pregnancy test was positive. All women were followed in a combined obstetric/coagulation clinic and seen by a thrombosis specialist every 2 months until 6 weeks post-partum. Anti-FXa levels were not routinely monitored in maternal and cord blood and doses of LMWH were not adjusted for increasing bodyweight or

increasing renal clearance. If hypersensitivity skin reactions developed, we either switched once to another preparation (tinzaparin or nadroparin), acenocoumarol or started fondaparinux 2.5 mg subcutaneously twice daily. Fondaparinux 7.5 mg once daily (therapeutic dosage) is not available in the Netherlands, and we wished to avoid thrice daily injections. The women had no standard planned induction with withholding of fondaparinux, but anticoagulation was stopped at the start of spontaneous labor and restarted 4–8 h after delivery (when blood loss was normal) and stopped 6 weeks post-partum. Data were systematically collected by the thrombosis physicians during pregnancy on an indication for anticoagulant therapy; start date of LMWH; trimester of switching to another LMWH, vitamin K antagonist or fondaparinux; bleeding and thrombo-embolic complications during pregnancy, delivery and post-partum period; side effects of anticoagulants; gestational age of delivery; blood loss during delivery; birth weight and neonatal bleeding/congenital abnormalities. National legislation and the ethical committee of our institution approve this type of studies without the need for review of the protocol. All women were informed about the risks of the off label use of fondaparinux during pregnancy and agreed with it. In this letter, we report on the 12 out of 190 pregnancies in 133 women in whom fondaparinux was used.

We treated 10 patients with fondaparinux during pregnancy and the puerperium in our institution, two of them during two pregnancies. Their median age was 30 years (range 26–34 years). Six of them had a history of VTE during combined oral contraceptive use, three patients had a history of an idiopathic VTE and one patient had a history of recurrent fetal loss. None of the patients had a history of allergy to LMWH. Eight patients were switched to fondaparinux in the 2nd

Table 1 Detailed patient characteristics

Case no.	Age	Indication for anticoagulation	Thrombophilia	Anticoagulation before fondaparinux	Trimester start fondaparinux	Gestational age at delivery	Birth weight (gram)	Blood loss during delivery (mL)	Last injection before delivery (hrs)
1	32	PE during COC	PS def type I/hetzg FV leiden	nadroparin	3rd	40 4/7	3670	200	25
1	34	PE during COC	PS def. type I/hetzg FV leiden	–	1st	40 4/7	4330	300	20
2	30	Idiopathic DVT	Hetzg FV leiden	tinzaparin	2nd	38 6/7	3450	700	> 12
3	30	Recurrent fetal loss	No	nadroparin	2nd	38 2/7	3570	1200*	48
3	32	Recurrent fetal loss	No	–	1st	39 0/7	3975	500	17
4	30	CVT during COC	No	nadroparin/VKA	2nd	42 0/7	3929	2000†	> 12
5	30	DVT during COC	No	nadroparin/tinzaparin	2nd	37 0/7	3070	400	22
6	32	Idiopathic DVT	No	nadroparin	2nd	40 3/7	3700	300	7
7	26	Idiopathic PE	No	nadroparin	2nd	33 5/7	1990/1795	1000†	7
8	28	DVT during COC	PS def.type III/hetzg FV leiden	nadroparin	2nd	37 6/7	3110	200	9
9	33	PE during COC	PS def type I	nadroparin	3rd	41 1/7	3795	300	31
10	29	DVT during COC	No	nadroparin/tinzaparin	2nd	42 0/7	3795	700	30

CVT, cerebral venous thrombosis; DVT, deep venous thrombosis; PE, pulmonary embolism; VKA, vitamin K antagonist; COC, combined oral contraceptive use; PS, protein S; def, deficiency; FV, factor V; hetzg, heterozygous. *Atony of uterus †Secondary caesarean section.

trimester and two patients during the 3rd trimester. All patients were started initially on nadroparin or tinzaparin, two used both preparations and one patient used a vitamin K antagonist during the 2nd trimester before switching to fondaparinux (see Table 1 for detailed information). In all cases, the indication for switching to fondaparinux was hypersensitivity skin reactions to LMWHs, consisting of itching, local redness or subcutaneous infiltrates localized at the injection sites. Two patients were treated during two pregnancies, both started fondaparinux in the first trimester of their second pregnancy. No hypersensitivity skin reactions to fondaparinux were seen and patients reported no other side effects. No early or late fetal losses occurred. The median gestational age at delivery was 39 weeks (range 33 5/7–42 0/7 weeks). One patient delivered preterm twins as a result of preterm prelabor rupture of the membranes. The median blood loss during delivery was 450 mL (range 200–2000 mL); three patients had a greater than 1000-mL blood loss. The patient with 2000 mL blood loss had an atony of the uterus; she received her last injection of fondaparinux more than 12 h before delivery. One patient had 1200 mL blood loss during a secondary caesarean section; she received her last injection 48 h before delivery. The third patient had 1000 mL blood loss because of atony of the uterus and a preterm delivery of a twin; she received her last injection 7 h before delivery. None of these women with a greater than 1000-mL blood loss needed a blood transfusion. Postpartum, 4–8 h after cessation of the bleeding, these patients restarted on fondaparinux 2.5 mg twice daily. No bleeding recurred after restarting the drug. None of the 13 infants had congenital abnormalities or neonatal bleeding. Their median birth weight was 3685 g (range 1795–4330 g). No minor or major bleedings or thromboembolic events were reported during the pregnancy or post-partum period.

We report on all 12 pregnancies in our centre in which fondaparinux was used during the past 6 years. These data are derived from a prospective cohort study. We show that fondaparinux was not associated with increased bleeding, thromboembolic complications or fetal abnormalities.

To our knowledge, this is the largest prospective study that reports on the use of fondaparinux during pregnancy. In concurrence with others [6–11], we did not observe hypersensitivity skin reactions using fondaparinux, although all women had had hypersensitivity skin reactions to LMWHs. Recurrence of hypersensitivity skin reactions when switching to another preparation of LMWH in pregnant women is a known phenomenon [1].

Fetal safety is an important issue when considering a new anticoagulant therapy in pregnancy. LMWHs do not cross the placenta, so can not cause teratogenicity or neonatal bleeding [13–15]. A study by Dempfle *et al.* [11] demonstrated that fondaparinux passes the placental barrier *in vivo*, resulting in low measurable anti-FXa levels in umbilical cord blood. That study described five pregnant women, in four of whom low anti-FXa levels were measured. These levels were approximately 1/10 the concentration in maternal plasma, which is well below the concentration required for effective anticoagulation

[16]. Neonatal bleeding did not occur in the infants of these women. In the fifth woman, no elevated anti-FXa level was measured, probably because she received her last injection of fondaparinux 22 h before delivery. Based on these data, fondaparinux has the potential to affect the fetus. In a recently published retrospective study by Winger *et al.* [17], 29 women with a history of unexplained recurrent fetal loss and infertility using fondaparinux 2.5 mg once daily during the 1st trimester of pregnancy were described. They reported no adverse events, in particular no fetal abnormalities. In the 13 infants in our study, no congenital abnormalities or bleeding occurred. Our data are obviously limited by the size of our study, although it is the largest prospective series reported. Of note, only two infants were exposed during the first trimester. A limitation of our study is the missing anti-FXa levels in maternal and cord blood during labor because of the possibility of passage through the placenta and the potential side effects for mother and child. Nevertheless, none of the children had neonatal bleeding or fetal abnormalities.

In conclusion, we report here an alternative treatment with fondaparinux in 12 pregnancies in 10 women who had hypersensitivity skin reactions to LMWH. Fondaparinux did not cause hypersensitivity skin reactions and was not associated with bleeding or other complications in the mother and child. However, given the limited data, the use of fondaparinux during the first trimester should still be avoided.

Addendum

H.M. Knol and K. Meijer conceived the study idea and all authors contributed to the study design, data abstraction and interpretation. H.M. Knol wrote the manuscript and all authors took part in its revision and approved the final version.

Disclosure of Conflict of Interests

The authors declare that there are no conflict of interest.

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High rates of symptomatic and incidental thromboembolic events in gastrointestinal cancer patients

R. SINGH, T. SOUSOU, S. MOHILE and A. A. KHORANA

James P. Wilmot Cancer Center, Department of Medicine, University of Rochester, Rochester, NY, USA

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The association of thromboembolism with cancer, although known for over a century, has gained increased attention in recent years. Thromboembolic complications include deep vein thrombosis (DVT), pulmonary embolism (PE) and arterial events including stroke and myocardial infarction. Cancer patients on active treatment are particularly at risk, with a recent study demonstrating a 47% increase in frequency in hospitalized cancer patients receiving chemotherapy [1]. There are significant consequences of venous thromboembolism (VTE) in the cancer patient, including an association with mortality, a high risk of recurrent VTE and a paradoxically high risk of bleeding complications [2–4]. Patients with gastrointestinal cancers in particular have amongst the highest rates of VTE [5,6].

One of the potential causes of the increased frequency of VTE is the improvement in the resolution of computed

tomography (CT) technology in recent years. In the United States, multidetector-row CT technology expanded considerably in the earlier part of this decade [7]. This has led to an increased frequency of incidentally detected thromboembolic events. Recent analyzes have explored the implications of such incidental events and it has been questioned whether these are truly asymptomatic events [8]. Additionally, in a recent retrospective analysis, 6-month mortality was similar in cancer patients with symptomatic or asymptomatic VTE but significantly higher in comparison to cancer patients without VTE [9]. These analyzes have focused primarily on incidental events. Little is known about the prevalence and relative proportion of symptomatic and incidental thromboembolic events.

The objective of the present study was to determine the prevalence and relative proportions of incidental and symptomatic thromboembolic events in high-risk cancer patients. We conducted a retrospective analysis of a cohort of consecutive patients with gastrointestinal cancers undergoing active treatment at the Gastrointestinal Cancer Program of the James P. Wilmot Cancer Center at the University of Rochester Medical Center from 1 July 2008 to 31 December 2008. Primary sites of cancer considered for inclusion were esophageal, gastric including gastro-esophageal junction, liver, biliary tract, pancreatic, small bowel, colon, rectum and anal. Histologic subtypes included adenocarcinomas, squamous cell

Correspondence: Alok A. Khorana, 601 Elmwood Ave, Box 704, Rochester, NY 14642, USA.

Tel.: +1 585 275 4797; fax: +1 585 273 1042.

E-mail: alok_khorana@URMC.rochester.edu

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